Brief overview of differences of sex development

Differences of sex development, often referred to as dsd, are a large and mixed group of conditions. Below we give an incomplete overview of some common and some les common conditions, with some very short descriptions. Parents have told us that it is helpful for them and their children to see the name of 'their' specific condition alongside all the other ways bodies can develop.

What's in a name?

We have used **the names that parents use**, whether it is the condition-specific name, or the protein/enzyme or gene that makes the body develop differently. We want parents, young people and children to 'recognise' the name that has been used to describe 'their' different sex development. We hope you will find that this is the place to get further information.

Our list might therefor be (a little bit) different from a typical medical way of listing conditions. We will continue to develop it with input from young people, families and healthcare professionals.

Numbers?

We have tried to give some information about **how often** different sex development happen. Sometimes all we can say is 'Rare' because we don't have a reliable way (not in the UK nor elsewhere) to keep track of numbers and the different types of diagnoses. Doctors, in the UK, Europe and internationally, are working together so we can get better statistics and a better understanding in this area so that psychological and medical healthcare can be better targeted. It's good to know that this applies to all rare conditions, not just dsd!

What does 'Rare' mean?
The medical definition of a 'rare' condition is when it occurs in less than 1 person out of every 2000 (this means: less than 1/2000).

It is helpful to know also that some conditions have "hotspots" in different countries – this means, there might be some areas where one or other conditions are seen more frequently, and others where conditions are seen very infrequently. So when looking at 'prevalence' (how often) be aware that this is variable and that numbers can change as our understanding of these conditions improves.

1.7% (1/60) and as common as red hair?
A description sometimes used in popular media is that different sex development is as common as red hair. That is not very accurate.
A more realistic statistic is **0.05%** (1/2000 - DSD, including Klinefelter, Turner and MRKH) or **0.02%** (1/5000 - DSD, babies born with genital difference and/o atypical reproductive organs).

Revisit if no diagnosis obvious

If, at first, the doctors are unable to work out the exact diagnosis, discuss this again with your doctor from time to time to check if there have been any changes in testing methods or knowledge which may give further answers. Testing methods are constantly improving, and a full diagnosis may be possible a few years down the line.
Sometimes a specific diagnosis or cause may not be found and a general term like "hypospadias" or "partial gonadal dysgenesis" is used.
Having a diagnosis doesn't change how your baby developed, but it can be helpful to understand the different sex development of your baby. It helps to plan and focus on a baby's short and long-term health care needs (e.g. it can help us understand how baby will experience puberty). And it helps us to focus on your baby's overall wellbeing and on how to explain development.

Do I have to understand this?

We know that (different) sex development is complex, and it can take time to learn about the different pathway your baby or child has taken. If you don't understand something, go back to your medical team. Always feel free to ask questions: all questions are good questions!

What is really helpful – and what this overview shows - is to remember that there are *many ways* a baby can develop differently. You are not alone in your hopes and your concerns.

And understanding how *your* baby developed (with or without a specific diagnosis) can be really helpful when you begin to think about talking to your child about their health and when considering how to use day-to-day situations as building blocks for your child's learning about how she or he developed.

From early on you can for example use child-friendly books about how bodies work and grow to teach your child about 'genes' and 'hormones' and try to talk about how w all have genes and hormones. As your child grows up they will get used to those words, and they won't be scary or strange. For more information on Talking to Children about DSD please visit the dsdfamilies website.

More info?

dsdfamilies is applying for funding to produce dedicated information hubs, with specific info per condition covering pre-natal development to puberty, what it means and how you can talk about it.

Do feel free to write to us on info@dsdfamilies.org with your questions and we will try to include those in our information hubs.

Please also note that as we are developing the website we will connect the information in the table below with the information in our 'Story of Sex Development' (Spring 2019).

Overview of Differences of Sex Development

The conditions are listed in a 'logical' way, following the various steps in the process of sex development.
Use the main picture of the 'Story of Sex Development' to help you understand the many ways bodies can develop.

General Terms		
Name	**Short description**	**Estimated numbers**
Genital difference (also called 'ambiguous')	Genitalia that look less typical and when it is not clear to an untrained healthcare professional whether baby is a boy or a girl and further investigations might be needed.	1/4500-1/5500 babies
Clitoromegaly	A girl with clitoromegaly is born with a clitoris that is larger than usual	1/10 000
Undescended testes (Cryptorchidism)	A boy born with no testes in the scrotum	3/10 premature baby boys; in general 3/100 baby boys are born with at least one undescended testis
Hypospadias	When the opening of the penis (the urethra) is not at the tip but along the bottom shaft of the penis. There is a huge range of how hypospadias can affect someone, e.g. mild (the opening is near the tip) or peno-scrotal (the opening at the base of the penis shaft) or anywhere in between. Only children born with peno-scrotal hypospadias would be supported and cared for in a difference of sex development context.	1/300 boys

Sex Chromosomes DSD		
Name	**Short description**	**Estimated numbers**
Klinefelter's syndrome	When a child has an extra X chromosome in all cells (47, XXY) or in some cells (46,XY/47,XXY). For more information about Klinefelter's please visit the website of the Klinefelter's Syndrome Association	1/500 – 1/1000 men
Turner syndrome	When a child has one X chromosome in all cells (45,X) or in some cells (45,X/46,XX). Other less common chromosome combinations are also possible. For more information about Turner please visit the website of the Turner Syndrome Support Society	1/2500 women
45,X/46,XY Gonadal Dysgenesis (sometimes called **Mixed Gonadal Dysgenesis** or Mosaicism)	Some cells in the body of a child with mixed gonadal dysgenesis (MGD) will contain 45 chromosomes, incl. a single X, while other cells contain 46 chromosomes, incl. an X and a Y. Most children with MGD develop as typical boys and many will never know they have MGD. A small number will be born with internal and external reproductive and genital structures that are less typical	1/10 000 (most develop as typical boys)

46,XY DSD

The gonads of baby are 'instructed' to develop as testes because of a gene on the Y chromosome, but how do the testes really develop?		
Name	**Short description**	**Estimated numbers**
Complete Gonadal Dysgenesis (sometimes called **Swyer** Syndrome)	The gonads of a baby in the womb with CGD remain undeveloped, so most of what is left of the gonads at the time of birth are small pieces of connective tissue. Because there are no testes producing AMH, babies will be born with fallopian tubes, a womb and a vagina (both usually less developed).	1/160 000
Partial Gonadal Dysgenesis (PGD)	The gonads of a baby in the womb with PGD may develop partially into testes. Parts of the testes will produce testosterone and AMH, and other parts will remain undeveloped (and not produce any hormone).	Rare (maybe 1/20 000 – 1/40 000)
Steroidogenic factor-1 deficiency **(SF1)** (also known as NR5A1)	SF1 is a protein important for the development of the gonads and the adrenal glands. Reduced SF1 function (this means: when SF1 is not working very well) in a baby in the womb may cause absence or incomplete development of the gonads. This in turn will influence how much testosterone and AMH is produced. SF1 is one know cause of gonadal dysgenesis. SF1 may also affect the development of the adrenal glands in some very rare circumstances.	Rare (maybe 10% of 46, XY DSD)
DAX1 (Duplication of genetic material on the X chromosome in the region that contains the NR0B1 gene)	A baby in the womb with DAX1 has an extra copy of the NR0B1 gene which prevents the formation of male reproductive tissues. DAX1 is a protein (coordinated by the NR0B1 gene) that acts as an 'anti-testis factor', maybe by acting against the SRY gene. It means that when SRY kickstarts the development of testes, the extra DAX1 proteins will try to stop this. This means that one or both testes will not develop fully.	Rare
Frasier Syndrome	Similar circumstances to partial gonadal dysgenesis – children may have some kidney problems in late childhood that become manifest by loss of small amounts of proteins (caused by changes in the Wilms Tumour/WT1 gene, but less likely to have/result in Wilms Tumour)	Rare
Denys-Drash syndrome	Similar circumstances to partial gonadal dysgenesis – children have a high risk of kidney cancer and losing protein in their urine in early life (Wilms Tumour/WT1)	Rare

Are the (under)/developed testes producing AMH (the hormone suppressing development of the womb and all internal typical female reproductive structures)? **Are the (under)/developed testes producing Testosterone and dihydroTestosterone /'super'-testosterone (the hormones that are required for typical male development on the inside and the outside)?**		
Name	**Short description**	**Estimated numbers**
Leydig cell hypoplasia (LCH)	The cells in the testes called Leydig cells that usually produce the hormone testosterone are underdeveloped (hypoplasia) or do not develop ('aplasia' or 'agenesis') in a baby in the womb. Children can have a complete and partial form of LCH.	Rare
STAR/CYP11A1	'Steroidogenic acute regulatory protein' (STAR) and CYP11A1 regulate the early stages of steroid production in the testis and adrenal gland. Absence or reduced function of these proteins means that no or less testosterone is produced whilst the baby is in the womb. The child also develops adrenal insufficiency, usually in the first few days or weeks of life.	Rare
3-Beta or 3β -HSD-2-deficiency	Baby has an absence or reduced function of the 3β -HSD-2 enzyme meaning that less testosterone than usual is produced whilst baby is in the womb	Rare
17alpha hydroxylase	Baby has an absence or reduced function of the 17α –hydroxylase enzyme meaning that less testosterone than usual is produced whilst baby is in the womb. This also results in an imbalance in adrenal steroids, which can cause features such as high blood pressure with age.	Rare
17- Beta or 17β -HSD-3-deficiency	Baby has an absence or reduced function of the 17β -HSD-3 enzyme meaning that no or reduced testosterone is produced whilst baby is in the womb. Some young girls with 17-Beta will only be diagnosed in teenage years when they do produce testosterone and their body is responding to androgens.	Rare (except in certain geographical areas)
5-alpha or 5α reductase type 2 deficiency	Baby has an absence or reduced function of the 5α reductase enzyme which is usually required to convert testosterone into 'super testosterone' (DHT). Some young girls with 5-alpha will only be diagnosed in teenage years when they do produce testosterone and their body is responding to androgens.	Rare (except in certain geographical areas)

Can the body respond to androgens? This means: the body can make the hormones, but does the body know what to do with the androgens/testosterone/dihydro Testosterone?

Name	Short description	Estimated numbers
Complete Androgen Insensitivity Syndrome (**CAIS**)	The body of a baby in the womb is *completely* insensitive to the androgen hormones (incl testosterone and DHT) that are produced because the 'androgen receptor' doesn't recognize the androgen hormones, or: does not know what to do with the androgens. Girls will usually only be diagnosed towards end of puberty when they don't have periods.	1/40 000 women
Partial Androgen Insensitivity syndrome (**PAIS**)	The body of a baby in the womb is *partially* insensitive to the androgens (incl testosterone and DHT) that are produced. This happens when the 'androgen receptor' only partially recognizes the androgen hormones, or: only knows a little bit of what to do with the androgens. Children can be diagnosed at birth or girls can be diagnosed in teenage years when they don't have periods or when their body responds partially to the androgens.	Rare
Persistent Mullerian Duct Syndrome (PMDS)	Boys are born with a typical penis, and they also have a uterus and fallopian tubes. The uterus and fallopian tubes are derived from a structure called the 'Müllerian duct' during development of the foetus. Testes are usually undescended as they are attached to these structures.	Rare
Testicular Regression Syndrome (vanishing testes syndrome)	Boys are born with a complete or partial absence of one or both testes but development of a typical penis or sometimes with hypospadias. This occurs when the testis regresses or is damaged in the later stages of pregnancy *after* the external structures have started to form. For more information you can contact the Anorchidism Support Group (UK).	1/20 000

46,XX DSD		
Name	**Short description**	**Estimated numbers**
Testicular DSD (46,XX)	The gonads of a baby in the womb develop as testes, often because of the 'translocation' of the SRY gene from the Y to the X chromosome. This means that, prior to fertilization, the SRY gene in the one fertilizing sperm 'breaks off' the Y chromosome and 'attaches' itself to another chromosome (usually the X). And the presence of the SRY gene then kickstarts the development of the gonads as testes.	1/20 000 men
Ovotesticular DSD (46,XX)	The gonads of a baby in the womb develop as ovotestes (this means part ovary and part testis). There may be differences in the amount of testis and ovary tissue on the left and right sides	1/100 000
Congenital Adrenal Hyperplasia 21-OHD (Majority of people with **46,XX CAH**)	A baby in the womb will develop ovaries and typical female internal reproductive organs. Baby has a reduced function of the 21-hydroxylase enzyme resulting in an increased production of androgens by *the adrenal glands*. This will sometimes affect the size of the clitoris of a newborn baby. Children often develop adrenal insufficiency and salt-loss a few days/weeks after birth. For more information and support, please also visit the Living with CAH support group (UK)	1/30 000 (46,XX children)
Congenital Adrenal Hyperplasia 11-beta-hydroxylase	A baby in the womb has a reduced function of the 11-hydroxylase enzyme resulting in an increased production of androgens by the adrenal glands. Because of an imbalance in adrenal hormones, children can develop high blood pressure with age. For more information and support, please also visit the Living with CAH support group (UK)	Rare (except in certain geographical areas)
Mayer-Rokitansky-Kuster Hauser **(MRKH)** syndrome	Women who have typical ovarian development and typical genitalia. The womb (uterus) and upper part of vagina do not develop. There are various dedicated MRKH information and support groups.	1/4000-5000 women

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